Autonomic functions and orthostatic responses 24 h after acute intense exercise in paraplegic subjects

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Engelke, Keith A., J. Darrell Shea, Donald F. Doerr, and Victor A. Convertino. Autonomic functions and orthostatic responses 24 h after acute intense exercise in paraplegic subjects. *Am. J. Physiol.* 266 (*Regulatory Integrative Comp. Physiol.* 35): R1189–R1196, 1994.—We tested the hypothesis that a bout of graded exercise designed to elicit maximal effort would increase the sensitivity of autonomically mediated baroreflexes and enhance blood pressure (BP) stability in subjects prone to postural hypotension. Therefore, we measured heart rate (HR), BP, forearm vascular resistance (FVR), and vasoactive hormone responses before and during 15 min of 70° head-up tilt (HUT) in 10 paraplegic subjects (21–65 yr) on two occasions: *1*) 24 h after maximal arm-crank exercise (postexercise) and *2*) without exercise (control). During HUT, HR increased 30 beats/min in both postexercise and control, but the reduction in systolic BP (SBP) during control (−12.0 ± 4.6 mmHg) was larger ($P = 0.017$) than that during HUT after exercise (−0.3 ± 4.3 mmHg). The postexercise increase in FVR from supine to HUT of 17.0 ± 2.4 to 24.8 ± 3.2 peripheral resistance units (PRU) was greater ($P = 0.042$) than the increase observed during control (18.3 ± 3.7 to 19.5 ± 3.1 PRU). The gain of the carotid-cardiac baroreflex was also increased ($P = 0.049$) after exercise. Responses in norepinephrine, vasopressin, and plasma renin-angiotensin induced by HUT were similar for control and postexercise, and there was no difference in either leg compliance or plasma volume between the two conditions. Additionally, HR and SBP responses to phases II and IV of the Valsalva maneuver, indexes of integrated baroreflex sensitivity, were increased ($P < 0.05$) after maximal exercise compared with control. Thus acute intense exercise eliminated orthostatic hypotension in paraplegics, was associated with increased FVR and baroreflex sensitivity, and was independent of blood volume changes.

baroreflex; blood pressure; cardiovascular reflex; head-up tilt; orthostatic hypotension; paraplegia

CARDIOVASCULAR REFLEXES mediated by the baroreceptors regulate cardiac output and systemic peripheral resistance to maintain mean arterial pressure during an orthostatic challenge. Because blood pressure varies as the product of heart rate, stroke volume, and vascular resistance, failure of these fast-acting autonomic reflexes to counteract orthostatically induced reductions in cardiac output can lead to hypotension and possible syncope. A disruption in the integrity of these reflexes has been associated with compromised blood pressure control after prolonged bed rest (6) and chair confinement (5), as indicated by an attenuation of orthostatic tachycardia and a reduction in the gain of the carotid-cardiac baroreflex (5, 6).

A single bout of dynamic exercise has been reported to increase the sensitivity of cardiovascular reflexes and enhance the maintenance of blood pressure during the postexercise recovery period. Acute graded exercise to exhaustion increased carotid baroreceptor stimulus-cardiac reflex response by 60 min postexercise (26) and lasted as long as 24 h after exercise (4, 8). A single bout of intense treadmill exercise at the end of 10 days of bed rest restored heart rate, blood pressure, and orthostatic stability to pre-bed-rest levels within 2 h of ambulation (3) and reversed fainting episodes after 6 h of water immersion (29). These observations suggest that exercise of this type can enhance the function of cardiovascular reflexes to maintain blood pressure during orthostasis and may provide effective countermeasure treatment for orthostatic hypotension. Therefore, we tested the hypothesis that a bout of dynamic maximal exercise would increase the sensitivity of autonomically mediated baroreflexes and enhance blood pressure stability during an orthostatic challenge. Paraplegic subjects were chosen because postural hypotension has been associated with prolonged wheelchair confinement (5). We recently reported that stable blood pressure during head-up tilt (HUT) 24 h after maximal exercise was associated with an increased sensitivity of the carotid-cardiac baroreflex (11). However, increased gain of this vagally mediated cardiac reflex response could not fully explain the elimination of orthostatic hypotension observed in the postexercise condition. Consequently, we now report integrated arterial and cardiopulmonary baroreflex responses as well as heart rate, blood pressure, forearm vascular resistance, leg compliance, and vasoactive hormones during 70° HUT in 10 paraplegic subjects 24 h after a bout of dynamic arm exercise.

METHODS

Subjects. Ten sedentary paraplegic subjects [age 36 ± 4 yr, height 185 ± 2 cm, and weight 90 ± 7 kg (means ± SE)] who had experienced traumatic spinal cord transection in the thoracic region (range of injury, T_1–T_{12}) gave their written consent to serve as subjects for this investigation after they had been informed of all procedures and risks. Subjects had been confined to their wheelchairs for an average of 118 ± 21 mo, and none had attained the upright posture for at least 6 mo before the beginning of the study. Selection of subjects was dependent on clinical results from a screening evaluation that included a detailed medical history and a physical examination. None of the subjects suffered from neuromuscular disease. All subjects were asked to abstain from exercise, tobacco, alcohol, caffeine, and medications not essential for the mainte-

nance of clinical stability for a minimum of 24 h before each experimental session.

Experimental design. Subjects completed two experimental protocols. Each protocol involved measurement of heart rate (HR), systolic (SBP) and diastolic blood pressures (DBP), forearm vascular resistance (FVR), and vasoactive hormone responses before and during 15 min of 70° HUT on 2 days: *1*) 24 h after acute intense exercise, and *2*) during a control (no exercise) condition. Additionally, measurements of plasma volume, carotid-cardiac baroreflex relationship, leg compliance, and hemodynamic responses to the Valsalva maneuver were made under the two experimental conditions. The test days were separated by 1 wk, and the two experimental conditions were given in random order.

Experimental protocol. On arrival at the laboratory, the subject was assisted out of the wheelchair and assumed the supine posture on a motorized tilt table in a quiet room for 30 min to establish a stabilized baseline for HR and blood pressure (BP). HR was measured from continuous beat-to-beat recording with an electrocardiogram telemetry system. BP was measured on the right arm by brachial artery auscultation, and mean arterial pressure was calculated by dividing the sum of SBP and twice DBP by three. After the baseline period, a blood sample was obtained from an antecubital venipuncture to determine plasma volume and pretilt circulating levels of norepinephrine (NE), arginine vasopressin (AVP), and plasma renin-angiotensin (PRA). After the blood sample, a test was conducted for measurement of the carotid baroreceptor stimulus-cardiac response relationship. Leg compliance and HR and BP responses to the Valsalva maneuver were also determined at this time. After these measurements, each subject underwent an orthostatic test on a tilt table.

70° HUT. A motorized tilt table elevated the subject to a 70° head-up posture within 10 s. Subjects remained in this position for 15 min or until the onset of presyncopal symptoms. During tilt, beat-to-beat HR was continually recorded. BP was measured on the right arm at 2-min intervals, while forearm blood flow was measured on the left arm according to the protocol described below. At the conclusion of the tilt, the subject was quickly returned to the supine posture, and a blood sample was drawn within 30 s to be analyzed for NE, AVP, and PRA. An identical procedure was repeated 1 wk later to measure the same variables under the remaining treatment condition.

FVR. FVR was calculated from the forearm blood flow measured by venous occlusion plethysmography with the use of a standard Whitney (mercury-in-Silastic) strain gauge placed around the maximal diameter of the left forearm. Circulation to the hand was occluded with a cuff placed at the distal end of the forearm, and venous efflux was impeded by a second occlusion cuff placed on the brachium just above the elbow. With blood flow to the hand occluded by inflation of the distal cuff to 250 mmHg, the brachial cuff was inflated to 30 mmHg for 10 s followed by 20 s of deflation. This sequence was repeated continuously throughout the 15 min of HUT. A total of 30 forearm blood flow measurements during HUT were averaged to provide one value representing mean forearm blood flow for that test. FVR was calculated by dividing the mean arterial pressure by forearm blood flow.

Leg compliance. Compliance of the left leg was measured during supine rest using a Whitney strain gauge placed at the point of greatest calf circumference. After 30 min of supine control, the left leg was slightly elevated (~4 in) at the ankle, and an occlusion cuff placed just above the knee was inflated to 30 mmHg for 120 s. Leg compliance was calculated by dividing the volume change (ml/100 ml) at a plateau (i.e., point at which venous pressure equals cuff pressure) by the cuff pressure and was expressed as [Δ(ml/100ml)]/Δ mmHg. The value for leg compliance was multiplied by 100 for convenience.

Blood samples. A 30-ml antecubital venous blood sample was taken without stasis before and at the end of each tilt test. Immediately after each withdrawal of blood, 21 ml of whole blood were taken from the vacutainer and transferred to a chilled tube containing sodium EDTA. The remaining 9 ml were introduced into a lithium heparinized tube. Whole blood was taken directly from the EDTA tube for triplicate microhematocrit measures (~0.5 ml) and for hemoglobin (~0.5 ml) using the Coulter S+4 system. The remaining EDTA-treated whole blood was centrifuged at 2,000 *g* for 15 min at 4°C. Immediately after centrifugation, plasma aliquots were measured for NE, AVP, and PRA and were stored at −60°C until hormonal assays were performed.

Hormone assays. Radioimmunoassay (RIA) procedures were used to analyze plasma for AVP (Instar Nuclear) and PRA (Biotecx RIA kit). For determination of AVP, samples were extracted using ODS-silica columns and were then assayed using a disequilibrium RIA procedure. The sample and first antibody were incubated for 18 h at 2–8°C. ^{125}I tracer was added followed by a second incubation at 2–8°C. A second antibody-precipitating complex was added for phase separation. The supernatant was then poured off, and the precipitate was counted in a gamma counter. Spiked recovery was 92%, sensitivity was 0.5 pg/ml, and within-assay and between-assay coefficients of variability were 2.8 and 9.9%, respectively. For determination of PRA, an EDTA plasma sample was adjusted to pH 6 with maleic acid. Phenylmethylsulfonyl fluoride and edetic acid were added to the plasma to act as inhibitors to prevent degradation of angiotensin I. Half of the sample was incubated in a 37°C water bath for 2 h, and the other half was kept in an ice bath at 4°C. The incubated portion reflects the circulating level plus the quantity of angiotensin I generated through the action of the renin in the plasma sample. The net quantity of angiotensin I at 37°C was calculated by subtracting the angiotensin I level in the 4°C sample from the angiotensin I level in the 37°C sample. Measurement of PRA was performed by a RIA competitive binding procedure using a specific antibody, a radiolabeled antigen, a pure sample of antigen used as a reference standard, and a separation medium. The amount of unlabeled antigen in the sample being analyzed was determined by comparing the assay results to a standard curve prepared with known amounts of the unlabeled antigen. Recovery efficiency was 96%, sensitivity was 0.1 $ng \cdot ml^{-1} \cdot h^{-1}$, within-assay coefficient of variability was 2.7%, and between-assay coefficient of variability was 5.5%. Plasma NE concentrations were measured by high-performance liquid chromatography (Waters). NE was extracted by absorbing plasma samples onto alumina. After the absorbed alumina was washed with a dilute buffer solution, catecholamines were eluted from the alumina when treated with an acidic solution. 3,4-Dihydroxybenzylamine was used as an internal standard, and extraction efficiency of NE was based on the extraction of known standards. After extraction, the samples were assayed using a Waters 712 Wisp to inject the samples onto a reverse-phase C_{18} column. A Waters 460 electrochemical detector was used to determine the concentrations of NE in the samples. The autoinjector and detector were interfaced with a Digital 380 computer using Waters software. The within-assay coefficient of variability was 1.4%, and the between-assay coefficient of variability was 3.8%.

Plasma volume. Plasma volume was measured with a modified Evans blue dye (T-1828) dilution method (14) using sterile solutions of Evans blue dye contained in 10-ml ampules (Macarthy Medical, Romford, Essex, UK). After each subject

was stabilized in the supine position for 20 min, an intravenous injection of dye was administered through a sterile 0.45-μm filter. (On the 2nd test day, a preinjection control blood sample was drawn followed by the intravenous injection of the dye.) Plasma (1 ml) from a 10-min postinjection blood sample was passed through a wood-cellulose powder (Solka-Floc SW-40A) chromatographic column so that the dye could be absorbed. The absorbed dye was eluted from the column using a 1:1 water-acetone solution (pH 7.0) and was collected in a 10-ml volumetric flask. The postinjection solution was compared with 1-ml samples from a preinjection time (0 control) and a standard dye solution (1:50 dilution with distilled water), and all samples were read at 615 nm with a spectrophotometer.

Valsalva maneuver. Subjects performed three Valsalva maneuvers according to a strict protocol at a controlled expiratory pressure of 30 mmHg. Each trial included a 30-s baseline period of quiet breathing, a 15-s strain period, and a 2-min poststrain period. After instruction in the technique and several practice runs, subjects were asked to take a normal inhalation and blow into a mouthpiece connected to a pressure transducer. A small leak in the system prevented the subject from maintaining the expiratory pressure by occluding the glottis. A pressure gauge positioned in front of the subject provided feedback on the expiratory pressure. Continuous HR and beat-to-beat BP responses were saved as a digital record, and data from the three trials were averaged. HR and BP changes during the four phases of the Valsalva maneuver (see Fig. 3; Ref. 16) were analyzed in a phase-by-phase manner (31). For comparison between experimental conditions, BP responses to each phase [change in SBP (ΔSBP)] were quantified as follows: *phase I*) peak SBP − baseline SBP (*point b − point a*); *phase II*) peak phase I SBP − lowest phase II SBP (*point c − point b*), and peak late phase II SBP − baseline SBP (*point d − point a*); *phase III*) peak phase II SBP − lowest phase III SBP (*point d − point e*); and *phase IV*) peak phase IV SBP − lowest phase III SBP (*point f − point e*). Changes in HR (ΔHR) were also determined during all four phases, as was the ratio of the unit change in HR to the unit change in SBP (ΔHR/ΔSBP) during phases II and IV because of its usefulness in describing integrated baroreflex function (17, 23, 25, 28, 30).

Carotid-cardiac baroreflex measurement. A neck-chamber device previously described (27) was utilized to evaluate the carotid stimulus-cardiac response relationship of the baroreflex. Stimuli were delivered to the carotid baroreceptor by a computer-controlled motor-driven bellows that provided pressure steps to a Silastic neck chamber covering the area of the carotid arteries. An initial pressure of 40 mmHg was delivered to the chamber and maintained for four R waves. With the next R wave, the pressure sequentially stepped to approximately 25, 10, −5, −10, −20, −35, −50, and −65 mmHg followed by a return to ambient pressure. Pressure steps were triggered by R waves so that neck-chamber pressures were superimposed on naturally occurring cardiac pulses. To avoid respiration-related variations of cardiac vagal outflow, we applied neck-pressure changes only while subjects held their breath at midexpiration.

A test session consisted of seven successful applications of the aforementioned neck-pressure sequences. Each sequence lasted ~15 s, and each test session lasted 15 min. Individual trials were discarded immediately if the subject breathed during the stimulus sequence or if the neck chamber failed to seal adequately. BP was measured with a sphygmomanometer before the application of the stimulus. Carotid distending pressure was calculated as systolic pressure minus neck-chamber pressure applied during each heart beat; this calculation assumes complete transfer of pressure in the neck chamber to the carotid arteries. The resulting stimulus-response relationship of the baroreflex was derived by plotting R-R intervals at each pressure step against their respective carotid distending pressure. From the average of each seven trials, baroreflex relationships were reduced to the determination of maximum slope to provide an index of reflex sensitivity. To determine the segment of steepest slope, we applied least-squares linear regression analysis to every set of three consecutive points on the response relationship.

Exercise bout. All subjects performed a multistage graded exercise bout designed to elicit a maximal effort utilizing a Monark arm-crank ergometer mounted on a table capable of being adjusted for the subject's seated height. After a 3-min warmup against no load, the work rate was set at 10 W and was increased by 5 W every 2 min. An electric metronome assisted the subject in maintaining a rotational cadence of 60–70 revolutions/min. This protocol was chosen because similar bouts of exhaustive exercise have been shown to increase baroreflex sensitivity (4, 26). HR was recorded during the last 15 s of each min while BP was measured by brachial artery auscultation before and immediately after cessation of exercise. The exercise bout was terminated when the subject reached volitional fatigue and was unable to maintain the required cadence for a period exceeding 15 s.

Statistical analysis. Standard descriptive statistics were performed on each of the response variables of interest with results presented as means ± SE. The average HR and BP response to HUT as well as baseline plasma volume, leg compliance, Valsalva maneuver, and carotid-cardiac baroreflex gain under the two treatment conditions were compared using paired-difference t statistics. NE, AVP, PRA, and FVR responses were compared with a repeated-measures two-way analysis of variance.

RESULTS

Exercise bout. For the 10 subjects, the final work rate at volitional fatigue averaged 38 ± 1 W and was attained after a mean time of 14 ± 1 min. HR, SBP, and DBP at termination averaged 175 ± 2 beats/min, 165 ± 2 mmHg, and 71 ± 1 mmHg, respectively.

Responses to 70° HUT. Supine SBP, DBP, HR, NE, AVP, PRA, and FVR before 70° HUT were not different between treatments (Table 1). During HUT, HR was elevated ($P = 0.001$) by 29 and 30 beats/min under control and exercise conditions, respectively. However,

Table 1. *Baseline hemodynamic, vasoactive hormone, plasma volume, and vascular resistance values during control and 24 h after high-intensity exercise*

	Control	Postexercise	P Value
HR, beats/min	61 ± 4	60 ± 6	0.427
SBP, mmHg	118 ± 5	116 ± 4	0.811
DBP, mmHg	77 ± 4	76 ± 4	0.568
Plasma NE, pg/ml	322 ± 53	304 ± 57	0.562
Plasma AVP, pg/ml	1.9 ± 0.1	1.9 ± 0.1	0.933
Plasma renin activity, ng·ml^{-1}·h^{-1}	0.77 ± 0.3	0.77 ± 0.2	0.775
Plasma volume, ml	3020 ± 132	3191 ± 210	0.459
Forearm vascular resistance, PRU	18.3 ± 3.7	17.0 ± 2.4	0.697

Values are means ± SE. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AVP, arginine vasopressin; PRU, peripheral resistance units.

during HUT in the control condition, SBP decreased ($P = 0.025$) from 118 ± 5 to 106 ± 9 mmHg, while there was essentially no change in SBP during HUT 24 h after maximal exercise (116 ± 5 to 113 ± 5 mmHg). Average reduction in SBP during control HUT (−12.0 ± 4.6 mmHg) was larger ($P = 0.017$) than that during HUT after exercise (−3.1 ± 3.9 mmHg). DBP during HUT was not altered in either condition.

Leg compliance. Left calf compliance in the postexercise condition was not different ($P = 0.438$) from that recorded during control period (1.8 ± 0.2 vs. 2.1 ± 0.4).

Circulating volume and hormone responses. NE, AVP, and PRA increased from supine to HUT ($P < 0.05$) but were similar for control and postexercise (Fig. 1). Plasma volume measured 24 h after acute exercise (3,020 ± 132 ml) was indistinguishable ($P = 0.459$) from the volume measured on the control day (3,191 ± 210 ml).

Baroreflex responses. As illustrated in Fig. 2, maximal exercise elicited greater ($P = 0.042$) FVR during HUT compared with the control condition. Pretilt baseline FVR was similar between control and exercise conditions and was highly correlated ($r = 0.84$; $P = 0.03$).

Mean HR and BP responses to the Valsalva strain in the control and postexercise conditions are illustrated in Fig. 3, *A* and *B*, respectively. Comparisons between HR and SBP changes during the four Valsalva maneuver phases are presented in Table 2. During late phase II, ΔSBP was fourfold greater ($P = 0.002$) 24 h postexercise than ΔSBP measured at a similar time in the nonexercise condition. Also, ΔHR/ΔSBP during phase IV was 40% greater ($P = 0.023$) in the postexercise condition (1.01 ± 0.14) than that during the control period (0.72 ± 0.11). There was no distinction between groups in ΔHR/ΔSBP during phase I. Phase III was brief and characterized by a reduction in SBP brought about by a decrease in mechanical compression of the thoracic cavity occurring as a result of the termination of the strain.

Mean carotid baroreflex stimulus-response relationships for all subjects during control and after exercise are illustrated in Fig. 4. Mean maximum slope of the carotid-cardiac baroreflex response was increased ($P = 0.049$) 24 h after intense exercise (6.2 ± 1.7 ms/mmHg) compared with the control condition (3.3 ± 0.6 ms/mmHg).

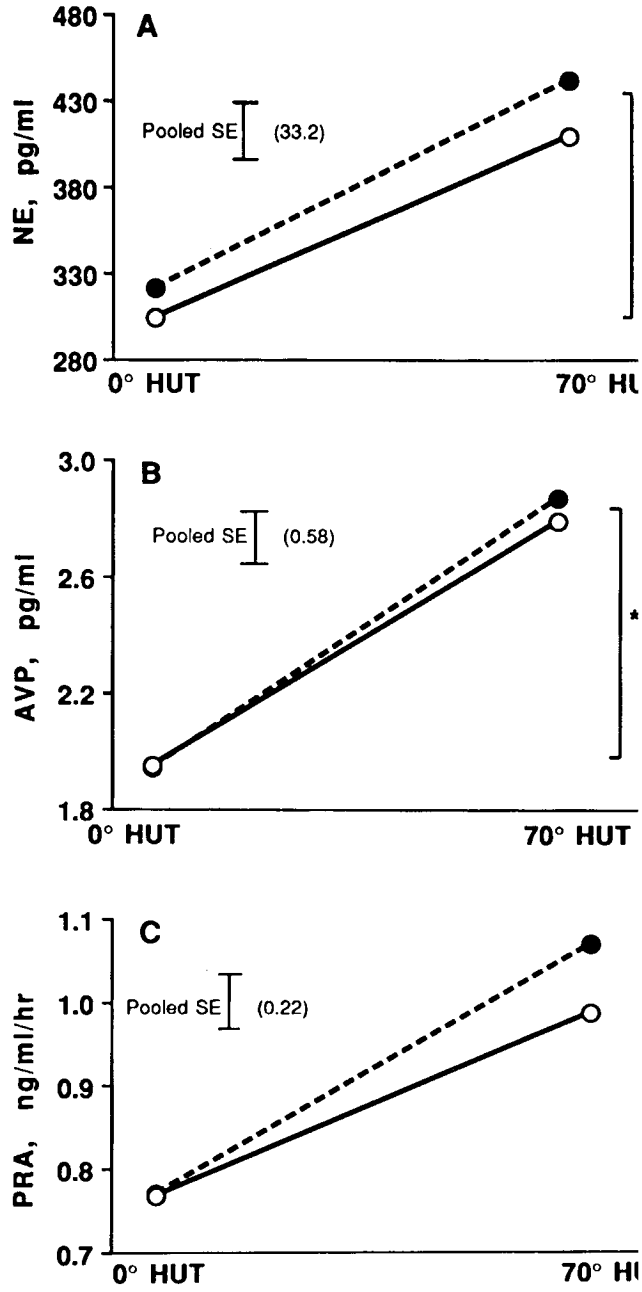

Fig. 1. Circulating norepinephrine (NE; *A*), arginine vasopre (AVP; *B*), and plasma renin-angiotensin activity (PRA; *C*) du supine (0°) baseline and at end of 70° head-up tilt (HUT) in con condition (○) compared with 24 h postexercise (●). *$P <$ (compared with corresponding supine values.

DISCUSSION

To test the hypothesis that acute exercise designed to elicit maximal effort can sensitize autonomically mediated cardiovascular reflex responses and ameliorate hypotension during an orthostatic challenge, we measured cardiac baroreflex responses and changes in HR, BP, FVR, and vasoactive hormones in response to 15 min of 70° HUT in paraplegic subjects 24 h after intense arm-crank exercise. The primary finding of this study was that 24 h after exercise, the elimination of orthostatic hypotension during 70° HUT was associated with increased baroreflex control of HR and FVR and was independent of changes in blood volume and leg compliance compared with the control condition. Furthermore, the observed improvement in systemic resistance occurred without alterations in circulating NE, AVP, a PRA.

A 10% expansion in plasma volume was induced 2 after the performance of maximal leg exercise in ambu tory subjects (13). If hypervolemia occurred in subjects, it is possible that the improved BP mair nance 24 h after exercise was associated with enhan cardiac filling (Frank-Starling effect). Against expec tions, plasma volume measured 24 h postexercise in subjects was not different than in the control conditi The lack of a hypervolemic effect is unclear but may

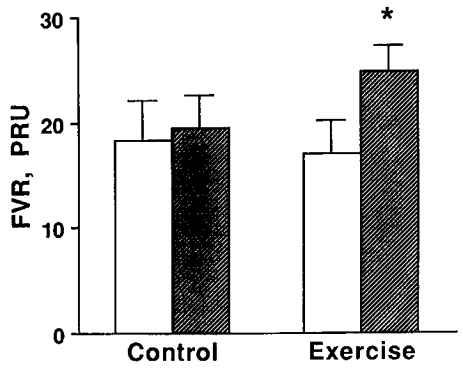

Fig. 2. Comparison of forearm vascular resistance (FVR) in supine posture (open bars) and after 15 min of 70° HUT (filled bars) in control and exercise conditions. Values are means ± SE. PRU, peripheral resistance units. $*P < 0.05$ vs. corresponding supine value.

associated with the lesser muscle mass and time to exhaustion involved in arm-cranking compared with leg exercise. In any event, improved BP stability during HUT 24 h postexercise could not be explained by blood volume changes.

Cardiac and hemodynamic responses during orthostatism may be influenced by leg venous compliance. An inverse relationship between leg compliance and tolerance to lower body negative pressure has been reported (18), suggesting that the capacity to maintain venous return, cardiac output, and systemic arterial pressure during an orthostatic challenge is dependent on the amount of blood pooled in the lower extremities. As expected with the abolishment of sympathetic outflow to leg vein and arterioles as well as muscle tone in these patients, leg compliance in the present study was similar between control and exercise conditions. This finding eliminated the possibility that maintained BP during HUT after exercise could be explained by differences in leg compliance. Unexpectedly, mean leg compliance measured in our paraplegic subjects (1.8 ml/mmHg) is approximately 30–60% less than values (2.6–4.4 ml/mmHg) reported for able-bodied subjects (7, 9). These comparisons raise the possibility that marked reductions in venous compliance in wheelchair-confined subjects may provide some protection against orthostatic challenge.

Because circulating vasoactive hormones, blood volume, and leg compliance were unaltered by exercise, increased sensitivity of reflexes mediated by baroreceptors probably represented the most contributing mechanism to the differences in maintenance of arterial pressure during HUT 24 h after exercise. Among these reflexes, it has been demonstrated that the sensitivity of the carotid-cardiac baroreflex can be increased for as long as 24 h after completion of a single bout of maximal exercise (4). Our present data not only confirm this finding but also provide evidence to suggest that baroreflex responses associated with control of vascular resistance are increased by exercise as well. SBP was maintained during 15 min of 70° HUT in the postexercise condition at a HR that was associated with hypotension in the control tilt. The absence of a difference in orthostatic tachycardia between the two experimental conditions implies that factors other than baroreflex control of cardiac responses were altered by exercise. Our observation of a greater FVR during postexercise HUT compared with control suggests that the responsiveness of vasoconstrictor mechanisms was enhanced by acute intense exercise and contributed significantly to postexercise maintenance of BP during tilt. However, the specific mechanism(s) responsible for the increased vasoconstriction remains to be identified.

With a crossover experimental design, we observed no distinguishable difference in the average baseline FVR between the control and exercise conditions, and test-retest comparisons for individual subjects were significantly correlated. These findings support the notion that occlusion plethysmographic measurement of FVR was highly reproducible from day to day and indicate that increased baroreflex response of FVR during HUT after exercise in this study was the result of the exercise treatment rather than some factor associated with methodology or time.

The mechanism by which FVR response during HUT was increased by acute exercise is unclear. Alterations in circulating volume can change cardiopulmonary baroreceptor control of vascular responses (32). Because vascular volume was not altered by the acute exercise in this study, it is unlikely that increased FVR during HUT after exercise could be explained by this mechanism. An

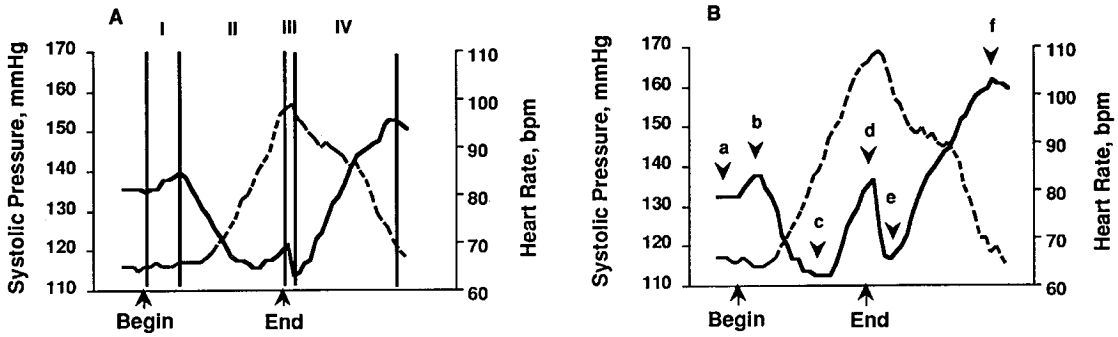

Fig. 3. Mean heart rate (dashed line) and systolic blood pressure (solid line) in response to a 15-s Valsalva maneuver at expiratory pressure of 30 mmHg in control (*A*) and 24-h postexercise (*B*) conditions. *A* also indicates the 4 phases (I–IV) of the Valsalva maneuver; *B* illustrates characteristic sample *points a–f* used for analysis (see *Valsalva maneuver*). bpm, beats/min.

Table 2. *Mean hemodynamic responses to a 30-mmHg Valsalva maneuver during control and 24 h postexercise*

	Control	Postexercise	*P* Value
Baseline HR, beats/min	66 ± 2	63 ± 3	0.252
Baseline SBP, mmHg	137 ± 4	134 ± 4	0.416
Phase I			
ΔHR, beats/min	−1 ± 0.4	−1 ± 0.3	0.477
ΔSBP, mmHg	3 ± 0.6	4 ± 0.7	0.338
ΔHR/ΔSBP, beats·min^{-1}·mmHg^{-1}	0.33 ± 0.1	0.25 ± 0.1	0.385
Phase II			
ΔHR, beats/min	33 ± 3	43 ± 2	0.003
Early ΔSBP, mmHg	−23 ± 3	−24 ± 2	0.576
ΔHR/early ΔSBP, beats·min^{-1}·mmHg^{-1}	1.4 ± 0.3	1.7 ± 0.3	0.559
Late ΔSBP, mmHg	−15 ± 4	4 ± 5	0.002
Phase III			
ΔHR, beats/min	−3 ± 1	−5 ± 2	0.287
ΔSBP, mmHg	−5 ± 1	−20 ± 2	0.001
Phase IV			
ΔHR, beats/min	−31 ± 6	−44 ± 6	0.005
ΔSBP, mmHg	44 ± 7	47 ± 6	0.739
ΔHR/ΔSBP, beats·min^{-1}·mmHg^{-1}	0.72 ± 0.11	1.01 ± 0.14	0.023

Values are means ± SE. ΔHR, change in HR; ΔSBP, change in SBP.

alternative explanation for greater postexercise FVR during tilt might be that exercise elicited a greater response of neural and humoral vasoactive agents such as NE, AVP, and PRA to orthostasis. It is widely documented that orthostasis causes increased plasma levels of NE (1, 2), AVP (2), and PRA (1, 2, 24) and that these hormone levels are associated with orthostatic tolerance (24). Elevations in plasma NE, AVP, and PRA in our subjects at the end of tilt were similar to those reported in paraplegics (15, 21, 22), and there were no differences in these responses between the exercise and control conditions. Therefore, increased FVR during HUT after acute intense exercise could not be explained by increased levels of these circulating vasoactive hormones. However, the observation that FVR was significantly increased during postexercise HUT at similar levels of circulating NE, AVP, and PRA may reflect that the exercise bout induced acute vascular receptor hypersensitivity to these neuroendocrine agents. This poss ity remains speculative without further investigat designed to pharmacologically assess alterations in cular receptor response.

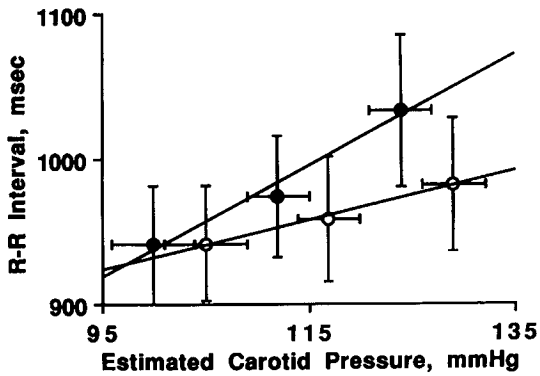

Fig. 4. Carotid-cardiac baroreflex stimulus-response relationships, plotted over range of pressures from which maximum slopes were derived, during control (○) and 24 h after exercise (●). Linear equation for control data is $y = 1.7x + 766$ ($r^2 = 0.987$) and for postexercise data, $y = 3.8x + 558$ ($r^2 = 0.975$). Values are means ± SE.

Tachycardia mediated by the baroreflexes provid means to buffer transient changes in arterial BP Data from both human and animal models have den strated that impairment of the carotid-cardiac refle associated with less tachycardia and occurrence of or static hypotension during upright posture (5, 6, 10 positive correlation has been reported between degree of impairment of baroreflex function and i dence of syncope during standing in healthy men a prolonged confinement to bed (6). Similarly, sinoao denervated dogs illustrated smaller HR increases greater BP reductions during upright posture than with intact baroreflexes (10). These results suggest if reductions in baroreflex function lead to attenu cardiac responses during an orthostatic challenge, t enhancement of baroreflex sensitivity should resu greater tachycardia and BP stability. With the use neck cuff device, the influence of a single bou exhaustive exercise on the cardioacceleratory limb o carotid-cardiac baroreflex was assessed from change HR from baseline values induced by an elevation of mmHg in cuff pressure. The consequent 40-mr reduction in carotid distending pressure elicited a ca lated elevation in HR of 5 beats/min (from 62 to during control and 7 beats/min (from 61 to 68) postexercise (Fig. 4). Thus, although increased car cardiac baroreflex sensitivity was relatively large consistent, it appears unlikely that vagally medi alterations in HR can completely explain the tachy dia noted during HUT. This raises the possibility other factors responsible for cardioacceleration, pos sympathetically mediated baroreflexes, were influe by exercise.

We used the ratio of the unit change in HR to the change in SBP (ΔHR/ΔSBP) during phases I, II, an of the Valsalva maneuver as an index of integr arterial baroreflex stimulus-response relationship. Δ ΔSBP represents an index of nonspecific baror control of HR because pressure reductions are like influence HR through interaction of cardiopulmor aortic, and carotid baroreceptor stimulation (17, 23 28, 30). Phase I occurs at the onset of the strain a characterized by an elevation in SBP and a s baroreflex-mediated bradycardia. The increase in SI considered to be mechanical in nature and prim dependent on the intensity of the maneuver and blood volume (28). Therefore, our observation of sir postexercise phase I ΔHR/ΔSBP compared with co is consistent with our finding of no difference in pl volume between the two experimental conditions.

Phase II of the maneuver is marked by an initial f SBP followed by a slight rise (Fig. 3). The fall in I accompanied by increases in HR and systemic vasc striction. These baroreflex-mediated actions preve further decline in BP and facilitate the late pha increase in pressure (23). Our subjects exhibit greater late phase II rise in SBP in the postexe

condition compared with control. Because total autonomic blockade substantially attenuated the increase in arterial pressure, the late rise in phase II SBP can be attributed to autonomically mediated reflex cardioacceleration and vasoconstriction (17). If this is true, then our results support the possibility that the 20-mmHg-higher SBP measured in our subjects during the postexercise condition was the result of enhanced autonomic function.

Phase IV represents the poststrain period, in which a reduction in HR is observed in conjunction with a rapid elevation in BP. In the control condition, an increase of 44 mmHg in SBP stimulated a 31-beats/min decrease in HR so that $\Delta HR/\Delta SBP$ was 0.72 beats $\cdot$ min^{-1} $\cdot$ mmHg^{-1}. Twenty-four hours after maximal exercise, an increase of 47 mmHg in SBP elicited a reduction in HR of 44 beats/min so that $\Delta HR/\Delta SBP$ was 1.01 beats $\cdot$ min^{-1} $\cdot$ mmHg^{-1}. Thus exercise induced a 40% increase in baroreceptor-cardiac reflex response. The change in HR during this phase of the Valsalva maneuver is thought to be mediated predominantly by sinoaortic baroreceptor-cardiac reflex activity (25). Clearly, the reduction in HR observed in the postexercise condition for a similar BP stimulus was markedly greater than that induced during the control test. Because carotid sinus baroreceptors do not singly contribute to the reflex control of HR (20), a portion of the enhanced cardiac reflex response during the postexercise Valsalva strain can be attributed to sensitized aortic baroreceptor control. This is reasonable because aortic baroreceptor-cardiac reflex has a more prominent role than the carotid baroreceptor-cardiac reflex in the control of HR (12, 19).

In summary, orthostatic hypotension during 15 min of 70° HUT was eliminated 24 h after completion of a single bout of exhaustive arm exercise in paraplegic subjects. Because exercise did not alter vascular volume, plasma levels of vasoactive hormones, or leg compliance, improved BP stability during HUT must be explained by increased sensitivity of autonomically mediated baroreceptor reflex control of cardiac and vascular responses. Indeed, maintenance of arterial pressure 24 h after acute intense exercise was associated with a heightened sensitivity of arterial baroreceptor stimulus-cardiac response relationships and greater FVR during HUT.

Perspectives

The development of hypotension and the possibility of frank syncope in astronauts after their return from spaceflight is an operational concern to the National Aeronautics and Space Administration. The orthostatic hypotension observed in paraplegic subjects and its relationship to the elimination of long-term exposure to the erect posture may be relevant to similar adaptations reported in astronauts exposed to prolonged microgravity. Both wheelchair confinement and spaceflight share the common feature of minimal variations in hydrostatic gradients that are routinely experienced by individuals during their normal daily activities of moving to and from standing postures. This commonality may underscore the importance of routine exposure to gravity-induced pressure gradients within the cardiovascular system as a primary stimulus for restoring normal function of baroreflexes and orthostatic stability on return to earth.

Acute exercise designed to elicit maximal physical effort is an attractive possibility for improving orthostatic stability after spaceflight by enhancing the responsiveness of baroreflex control of cardiac function and vascular resistance. The observation that this method was effective in individuals who have been confined from upright posture for months to years raises the intriguing issue that its application to astronauts after prolonged spaceflight may be effective. Operationally, the use of less frequent and more intense exercise as a possible countermeasure against postflight orthostatic hypotension is attractive because its use within 24 h of orbiter reentry would be maximally cost effective by enhancing crew safety and postflight recovery while minimizing inflight use of work time, food, water, and oxygen usually utilized during longer exercise regimens repeated during numerous days of the mission. The success of arm exercise observed in the present study is also attractive because the arms represent the primary muscle group used for mobilization and work in a microgravity environment. Clearly, the results from the present study provide a physiological basis for future groundbase and spaceflight testing of acute maximal exercise as a protective measure against postflight orthostatic instability in astronauts.

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